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Research Article

Comparison of the Efficacy of Dual Chemotherapy Regimens in Second-Line Treatment of Metastatic Esophageal Squamous Cell Carcinoma

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Abstract

Objectives: This study aimed to compare the efficacy of folinic acid plus 5-fluorouracil plus irinotecan (FOLFIRI), carboplatin plus paclitaxel, and cisplatin plus 5-FU regimens in second-line treatment of metastatic esophageal squamous cell cancer.

Methods: The study included patients over the age of 18 with a diagnosis of esophageal squamous cell carcinoma, stage 4 disease, who had progressed after first-line chemotherapy treatment for metastatic disease and received a dual chemotherapy regimen as a second-line chemotherapy.

Results: The mean age of 58 patients was 56.4±12.3 years and 33 (56.9%) of them were women. Among 58 patients, 18 received carboplatin plus paclitaxel, 25 received cisplatin plus 5-FU and 15 received FOLFIRI regimen. Second-line chemotherapy responses were 6.9% complete, 41.4% partial, 17.2% stable, and 34.5% of the patients developed progression. The median follow-up was 4.5 mo (0-46 mo). The median OS for all cohort was 14 mo (95% CI, 4.38-23.62) and there was no statistically difference between three groups (p=0.737).

Conclusion: In our study, we observed that doublet chemotherapy regimens were effective in the second series treatment of metastatic squamous cell carcinoma and may be a good option for patients with good performance status and no access to immunotherapy.

Keywords: Chemotherapy, esophageal squamous cell carcinoma, second-line treatment

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Esophageal cancer is the seventh most common cancer worldwide and the sixth most common cause of cancer-related deaths, causing more than 500,000 deaths worldwide annually.[1] It is also expected to cause 880 thousand deaths in 2040.[2] In the USA, 21,560 new cases and 16,120 deaths are expected in 2023.[3] Squamous cell carcinoma (SCC), the most common subtype, accounts for approximately 85% of cases.[4] Esophageal cancers are often not diagnosed at an early stage and are associated with high mortality, with more than one-third of patients diagnosed at the metastatic stage.[5] 5-year survival rates for metastatic disease are approximately 5%.[6] Unfortunately, a significant proportion of patients diagnosed in the locally advanced stage relapse despite multimodal therapies.[7, 8]

European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) Guidelines recommend chemotherapy (CTX) plus immunotherapy treatment for patients who are not suitable for local treat-

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ment and who can access immunotherapy in the first-line for systemic treatment. The standard treatment for patients who cannot access immunotherapy is conventional chemotherapy.[9, 10] The median survival with conventional chemotherapies is around 1 year.[11, 12]

In patients who develop progression after first-line treatment, NCCN and ESMO guidelines recommend second-line systemic treatment for patients who maintain a good Eastern Cooperative Oncology Group (ECOG) performance status. In patients who do not receive immunotherapy in the first-line treatment, immunotherapy is recommended in the second-line treatment. For patients receiving immunotherapy in the first-line, taxan or irinotecan treatments are recommended in the second-line.[9, 10] This recommendation is based on the results of small single-arm phase II studies with paclitaxel,[13] docetaxel,[14] irinotecan,[15] and data from retrospective cohort studies.

In the phase III KEYNOTE-181 study, the immunotherapy drug pembrolizumab improved overall survival compared to chemotherapy regimens in second-line treatment of advanced esophageal cancer with positivity of 10% or higher for programmed death-ligand 1 (PD-L1)[16] and was approved by the Food and Drug Administration (FDA) based on this study.[17] Also in 2019, the ATTRACTION-3 study demonstrated the superiority of the programmed cell death protein 1 (PD-1) inhibitor nivolumab over taxanes (paclitaxel or docetaxel) in overall survival in second-line treatment of advanced esophageal SCC patients.[18] Based on the results of this study, the FDA has approved patients with metastatic esophageal SCC who have progressed from previous fluoropyrimidine and platinum-based chemotherapy.[19]

Although cytotoxic first-line therapy is a widely accepted treatment strategy for advanced esophageal SCC, the benefit of second-line chemotherapy is uncertain. Our study aimed to compare the efficacy of folinic acid plus 5-fluorouracil plus irinotecan (FOLFIRI), carboplatin plus paclitaxel, and cisplatin plus 5-fluorouracil (5-FU) regimens in second-line treatment in patients who progressed after first-line cytotoxic chemotherapy.

Methods

Patients with esophageal squamous cell carcinoma who were treated at the oncology clinic of Van Yüzüncü Yıl University Medical Faculty Dursun Odabaşı Medical Centre between 2018 and 2020 were retrospectively included in our study. The study included patients over the age of 18 with a diagnosis of esophageal squamous cell carcinoma, stage 4 disease, who had progressed after first-line chemotherapy treatment for metastatic disease and received a dual chemotherapy regimen as a second-line chemotherapy. Patients younger than 18 years old and those who received single-agent chemotherapy, had missing data, and had more than one primary malignancy were excluded.

Patients were divided into three groups: FOLFIRI, cisplatin and 5-fluorouracil, and carboplatin and paclitaxel, according to the second-line chemotherapy regimen. Progression-free survival (PFS) was calculated as the time from the start of second-line treatment to the date of disease progression, or the time from the date of death, or the date of the last presentation in non-progressing patients. Overall survival (OS) was calculated as the time from the start of second-line treatment to the date of death or last follow-up. Patients were stratified as tumor differentiation (good-moderate-low), tumor localization (proximal-middle-distal), and ECOG performance score (0-1vs 2). Treatment regimens are as follows; FOLFIRI (irinotecan 180 mg/m^2 day one, leucovorin 400 mg/m^2 as a two-hour infusion and 5-fluorouracil 400 mg/m^2 as bolus, day one and day two followed with 1,200 mg/m^2/day as 22-hour continuous infusion). Carboplatin (AUC:2) and paclitaxel 60 mg/m^2 intravenously on days 1, 8, and 15 of every 28-day cycle. Cisplatin 75 mg/m2 day 1, 5-FU 750 mg/m2 1-4 days.

Categorical variables were presented as numbers (percentage) and continuous variables were presented as mean±SD. The compliance of the numerical values to the normal distribution was examined using histograms and the Kolmogorov-Smirnov test. Since quantitative variables were normally distributed, more than two independent groups were compared using the one-way ANOVA test. The Chi-square test was used to compare the proportions in three groups and post hoc analyses were evaluated with Bonferroni correction. Survival analyses were conducted using Kaplan-Meier from the start of second-line chemotherapy, and comparisons were made using the Log-Rank test. Prognostic factors for survival were investigated with Cox regression analysis. A p-value less than 0.20 in univariate analysis was included in the multivariate regression model. An overall p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA).

All procedures conducted within research involving human participants adhered to the ethical guidelines set by the institutional and/or national research committee, aligning with the principles outlined in the 1964 Helsinki declaration and its subsequent revisions, or equivalent ethical norms. The study was approved by the ethics committee of Van Research and Training Hospital, University of Health Sciences.

Results

The mean age of 58 patients was 56.4±12.3 years and 33 (56.9%) of them were female. Among 58 patients, 18 received carboplatin and paclitaxel, 25 received cisplatin and 5-fluorouracil, and 15 received FOLFIRI regimen. Regarding the location of the tumors, 13.8% were proximal, 62.1% were middle and 24.1% were distal. The second-line chemotherapy responses were as follows: 6.9% complete, 41.4% partial, 17.2% stable, and 34.5% of the patients experienced progression. The characteristics and results of the patients are summarized in Table 1. All patients have good performance status (ECOG 1-2). There was a higher incidence of hypertension in the carboplatin-paclitaxel group compared to the cisplatin and 5-fluorouracil group. Additionally, there were more patients with an ECOG PS of 2 in the carboplatin-paclitaxel group than in the FOLFIRI group (Table 1).

The median follow-up was 4.5 mo (0-46 mo). The median PFS for all cohorts was 6 mo (95% CI, 4.45-7.55) and there was no statistical difference between the three groups (p=0.241) as shown in Figure 1. The median OS for all cohorts was 14 mo (95% CI, 4.38-23.62) and there was no statistical difference between the three groups (p=0.737)

Table 1. Baseline characteristics of patients

Characteristics	Total n=58 (%)	Carbo-Pacli n=18 (31%)	Cis-5FU n=25 (43.1%)	FOLFIRI n=15 (25.9%)	p
Age, mean±SD	56.4±12.3	61.3±11.2	52.5±11.7	56.9±13.1	0.067
Gender, n (%)					0.303
Female	33 (56.9)	11 (61.1)	16 (64)	6 (40)	
Male	25 (43.1)	7 (38.9)	9 (36)	9(60)	
Smoking					
Yes (packet/year)					
Mean±SD	27.8±13.6	18.8±8.5	31.7±17.9	30±0	0.316
No, n (%)	43 (74.1)	14 (77.8)	18 (72)	11 (73.3)	
Hypertension, n (%)	15 (25.9)	10 (55.6)	2 (8)	3 (20)	0.002*
Diabetes mellitus, n (%)	7 (12.1)	4 (22.2)	2 (8)	1 (6.7)	0.342
Ischemic heart disease, n (%)	8 (13.8)	5 (27.8)	1 (4)	2 (13.3)	0.084
Differentiation, n (%)					0.766
Good	3 (5.2)	0	2 (8)	1 (6.7)	
Moderate	46 (79.3)	15 (83.3)	20 (80)	11 (73.3)	
Low	8 (13.8)	3 (16.7)	3 (12)	2 (13.3)	
Undifferentiated	1 (1.7)	0	0	1 (6.7)	
Localization, n (%)					0.549
Proximal	8 (13.8)	2 (11.1)	4 (16)	2 (13.3)	
Middle	36 (62.1)	12 (66.7)	17 (68)	7 (46.7)	
Distal	14 (24.1)	4 (22.2)	4 (16)	6 (40)	
ECOG PS, n (%)					0.008†
1	34 (58.6)	6 (33.3)	15 (60)	13 (86.7)	
2	24 (41.4)	12 (66.7)	10 (40)	2 (13.3)	
Second-line CTX response, n (%)					0.923
Complete	4 (6.9)	1 (5.6)	3 (12)	0	
Partial	24 (41.4)	7 (38.9)	10 (40)	7 (46.7)	
Stable	10 (17.2)	4 (22.2)	4 (16)	2 (13.3)	
Progression	20 (34.5)	6 (33.3)	8 (32)	6 (40)	
Progression, n (%)	39 (67.2)	12 (66.7)	18 (72)	9 (60)	0.679
Final situation, n (%)					0.201
Alive	22 (37.9)	9 (50)	10 (40)	3 (20)	
Dead	36 (62.1)	9 (50)	15 (60)	12 (80)	

Carbo-Pacli: Carboplatin and paclitaxel, Cis-5FU: Cisplatin and 5-fluorouracil, FOLFIRI: Folinic acid, 5-fluorouracil, and irinotecan, SD: Standard deviation, ECOG PS: Eastern Cooperative Oncology Group performance status, CTX: Chemotherapy.

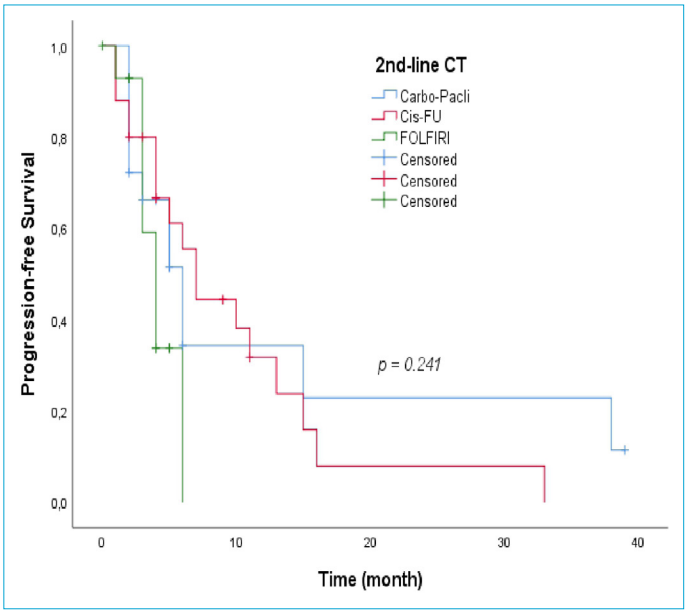

Figure 1. Survival curve for PFS comparison between chemotherapy regimens.

PFS: Progression-free survival, Carbo-Pacli: Carboplatin and paclitaxel, Cis-FU: Cisplatin and 5-fluorouracil, FOLFIRI: Folinic acid, 5-fluorouracil, and irinotecan, CTX: Chemotherapy.

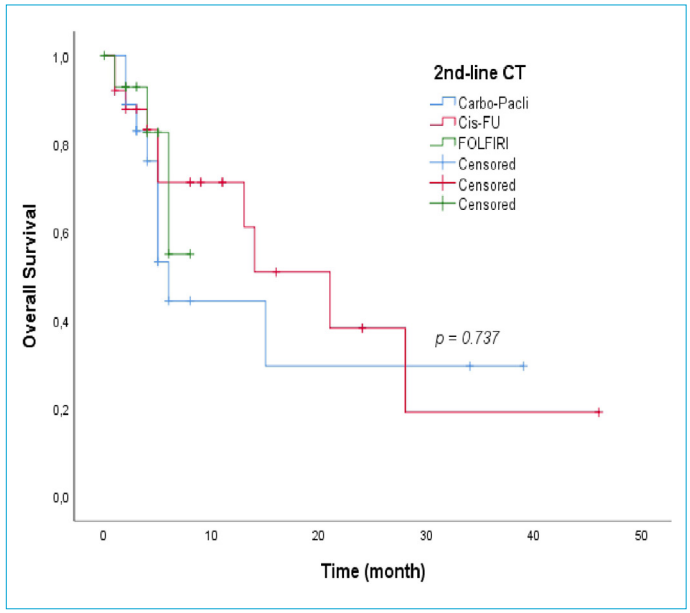

Figure 2. Survival curve for OS comparison between chemotherapy regimens.

OS: Overall survival; Carbo-Pacli: Carboplatin and paclitaxel; Cis-FU: Cisplatin and 5-fluorouracil; FOLFIRI: Folinic acid, 5-fluorouracil, and irinotecan; CTX: Chemotherapy.

as shown in Figure 2. In univariate analysis, ECOG PS was a statistically significant factor for OS, but not for age, gender, hypertension, diabetes mellitus, and second-line CTX regimen. In multivariate analysis, ECOG PS was found to be a prognostic factor (Table 2).

Discussion

In our study, we examined the efficacy of the treatment regimens used in patients who progressed after the first series of chemotherapy and were treated with dual chemotherapy in the second series. In our study, we did not find

Table 2. Prognostic factors for overall survival

Characteristics	Univariate Analysis			Multivariate analysis		
	p	HR	CI 95%	p	HR	CI 95%
Age	0.756	0.99	0.96-1.03			
Gender						
Male	ref			ref		
Female	0.120	2.12	0.82-5.44	0.053	2.74	0.99-7.61
Hypertension	0.099	2.19	0.86-5.59	0.472	1.62	0.43-6.07
Diabetes Mellitus	0.120	2.26	0.81-6.29	0.656	0.73	0.18-2.92
ECOG PS						
1	ref			ref		
2	0.001	26.45	3.55-197.05	0.001	30.37	3.99-230.81
Second-line CTX regimen						
Carbo-Pacli	0.751					
Cis-5FU	0.496	0.73	0.29-1.81			
FOLFIRI	0.585	0.69	0.18-2.62			

HR: Hazard ratio, CI: Confidence interval, ECOG PS: Eastern Cooperative Oncology Group performance status, CTX: Chemotherapy, Carbo-Pacli: Carboplatin and paclitaxel, Cis-5FU: Cisplatin and 5-fluorouracil, FOLFIRI: Folinic acid, 5-fluorouracil, and irinotecan.

any significant difference between FOLFIRI, cisplatin plus 5-FU, and carboplatin plus paclitaxel regimens in terms of both PFS and OS.

Only one-third of patients receiving first-line treatment can receive second-line treatment.[20] In patients who can receive treatment, treatment options are limited. A Cochrane database meta-analysis analyzing five randomized trials showed that the addition of systemic therapy to supportive care improves the quality of life and prolongs survival in metastatic esophageal cancer patients.[21]

In a phase III study published in 2020, evaluating the efficacy of pembrolizumab, a PD-1 inhibitor, 628 patients with both squamous cell and adenocarcinomas of the esophagus, who had progressed after a series of chemotherapy, were randomized 1:1. Half of the patients received pembrolizumab, while the other half received paclitaxel, docetaxel, or irinotecan-based on the physician's preference. Median survival was found to be 9.3 months in the pembrolizumab group and 6.7 months in the chemotherapy group.[16] In a phase III study evaluating nivolumab, another PD-1 inhibitor, 419 patients with a diagnosis of locally advanced or metastatic esophageal SCC who had previously received at least one serial treatment were randomized 1:1. One group of patients received nivolumab and the other group received weekly paclitaxel or docetaxel every 21 days. The primary endpoint of the study was overall survival, which was 10.9 months in the nivolumab group and 8.4 months in the chemotherapy group.[16] Compared to conventional chemotherapies, nivolumab, and pembrolizumab have been shown to increase survival in phase 3 trials and have started to be preferred, but due to the costs of these new drugs, a significant part of the world has problems in accessing these drugs and conventional chemotherapies continue to be used in second-line treatment.

In a retrospective study of 163 patients, paclitaxel and docetaxel were given to the patients. In the paclitaxel group, median PFS was 2.3 months and median OS was 6.1 months, while median PFS was 2.3 months and median OS was 5.3 months in patients who received docetaxel.[22] In a retrospective study comparing taxanes and non-taxanes in the second series, the median OS was 7.3 months in taxanes and 5.1 months in non-taxanes.[23]

In our study, the median OS was 14 months in the whole cohort and there was no statistically significant difference between the three groups (p=0.737). Median PFS was 6 months and again there was no statistically significant difference between the three groups (p=0.241). In our study, both PFS and OS were found to be longer than in previous studies evaluating chemotherapies. Single-agent chemotherapy was generally used in studies evaluating second-line treatments. We think that the reason for the longer PFS in our study is that we included only patients who received dual chemotherapy in our study.

The most significant limitations of our study are that it was designed as a single-center study, and the side effect data for the regimens used could not be accessed due to its retrospective nature. Additionally, the relatively small number of cases is a limitation. However, the fact that our study is the first to compare dual regimens in this patient group, and the observation that both PFS and OS values were longer than expected, adds value to our study.

Conclusion

In our study, we observed that doublet chemotherapy regimens were effective in the second series treatment of metastatic squamous cell carcinoma. Based on these findings, we believe that doublet chemotherapy regimens may be a good option for patients with good performance status and no access to immunotherapy. However, we also believe that our study results should be confirmed with studies including a larger number of cases.

Disclosures

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and approval was granted by the Ethics Committee of Van Research and Training Hospital, University of Health Sciences (Ethics no: 2023/14 – 02).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – G.G.; Design – G.G., Y.S.; Supervision – Y.S.; Materials – G.G., Y.S.; Data collection &/or processing – G.G., Y.S.; Analysis and/or interpretation – G.G., Y.S.; Literature search – G.G.; Writing – G.G.; Critical review – G.G., Y.S.

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